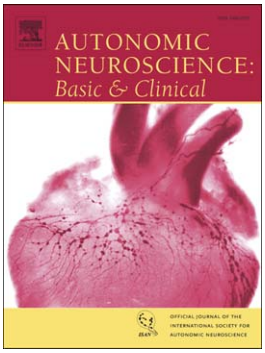
The influence of age and weight status on cardiac autonomic control in healthy children

Eyre, E L J; Duncan, M J; Birch, S L; Fisher, James

DOI:
10.1016/j.autneu.2014.09.019



The influence of age and weight status on cardiac autonomic control in healthy children: A review

E.L.J. Eyre, M.J. Duncan, S.L. Birch, J.P. Fisher

PII: S1566-0702(14)00155-6
DOI: doi: 10.1016/j.autneu.2014.09.019
Reference: AUTNEU 1694

To appear in: *Autonomic Neuroscience: Basic and Clinical*

Received date: 29 April 2014
Revised date: 12 August 2014
Accepted date: 25 September 2014

Please cite this article as: Eyre, E.L.J., Duncan, M.J., Birch, S.L., Fisher, J.P., The influence of age and weight status on cardiac autonomic control in healthy children: A review, *Autonomic Neuroscience: Basic and Clinical* (2014), doi: 10.1016/j.autneu.2014.09.019

The influence of age and weight status on cardiac autonomic control in healthy children: a review

Eyre ELJ[1], Duncan MJ[1], Birch SL[1], & Fisher JP[2]

[1] Department of Applied Science and Health, Biological and Exercise Sciences, Coventry University, James Starley Building, Priory Street, Coventry, CV1 5FB, United Kingdom.

[2] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom.

Address for correspondence:

Emma Eyre

Department of Biomolecular and Sport Science

Coventry University

Priory Street

Coventry

CV1 5FB

United Kingdom

Email: emma.eyre@coventry.ac.uk

ABSTRACT

Heart rate variability (HRV) analyses can provide a non-invasive evaluation of cardiac autonomic activity. How autonomic control normally develops in childhood and how this is affected by obesity remains incompletely understood. In this review we examine the evidence that childhood age and weight status influence autonomic control of the heart as assessed using HRV. Electronic databases (Pubmed, EMBASE and Cochrane Library) were searched for studies examining HRV in healthy children from birth to 18 years who adhered to the Task Force (1996) guidelines. Twenty-four studies met our inclusion criteria. Seven examined childhood age and HRV. A reduction in 24-hour LF:HF was reported from birth to infancy (1 year), while overall HRV (SDNN) showed a marked and progressive increase. From infancy to early-to-late childhood (from 12 months to 15 years) LF:HF ratio was reported to decline further albeit at a slower rate, while RMSSD and SDNN increased. Twenty studies examined the effects of weight status and body composition on HRV. In a majority of studies, obese children exhibited reductions in RMSSD (n=8/13), pNN50% (n=7/9) and HF power (n=14/18), no difference was reported for LF (n=10/18), while LF:HF ratio was elevated (n=10/15). HRV changes during childhood are consistent with a marked and progressive increase in cardiac parasympathetic activity relative to sympathetic activity. Obesity disrupts the normal maturation of cardiac autonomic control.

Key words: Heart rate variability, parasympathetic, sympathetic, child, obese

[1] **Abbreviations**

BMI - body mass index, **HF** - high frequency, **HRV** - heart rate variability, **LF** - low frequency , **LF/HF** - the low frequency to high frequency ratio, **NN** - normal-to- interval, **NU** - normalised units, **pNN50%** - proportion of RR intervals differing by >50 ms from previous RR interval, **QIS**- Quality index score, **RMSSD** - square root of the mean of the sum of successive differences, **SDANN** - standard deviation of 5 minute average RR interval over a 24 hour period, **SDNN** - standard deviation of all NN intervals, **ST** - short term, **TINN** - triangular interpolation of NN interval histogram.normal RR

1.1 BACKGROUND

Childhood obesity remains a global public health issue (WHO, 2010). Obesity raises the risk of developing chronic cardiovascular and metabolic disorders (Nguyen et al., 2008) and although previously considered as adult conditions their prevalence is on the rise in children (Whincup et al., 2002). Furthermore, once established in childhood these conditions have been reported to track to adulthood (Raitakari et al., 2003; Whincup et al., 2002). Autonomic dysfunction is prevalent in adults with cardiovascular disease and metabolic disorders (e.g., obesity, hypertension, type II diabetes) and contributes to the underlying pathophysiological processes (Abbound et al., 2012). In contrast to the wealth of data concerning the autonomic control of the heart in adult populations, much less work has been conducted in children. Thus, how cardiac autonomic control normally develops during childhood and how this may be affected by pathophysiological conditions, such as obesity, remains incompletely understood.

Since the 1970s several metrics have been developed to quantify the beat-by-beat fluctuations in heart rate (Kleiger et al., 2005; Task Force, 1996). Such indices of heart rate variability (HRV) can provide a valuable non-invasive insight into cardiac autonomic control (Task Force, 1996) and have prognostic utility as an indicator of cardiovascular risk in adult (Dekker et al., 2000; Thayer et al., 2010; Tsuji et al., 1996) and paediatric (Lammers et al., 2010) populations. Indeed, there is strong evidence to suggest that increased cardiac sympathetic drive is arrhythmogenic (Lown & Verrier, 1976), while high levels of cardiac parasympathetic are cardioprotective (Billman, 2006). HRV represents an attractive means of examining how age influences cardiac autonomic control in healthy children. An age-related alteration in HRV might be expected as a consequence of a multitude of mechanisms, including changes in heart rate, respiratory rate, growth and maturation, hormones, arterial

baroreflex sensitivity, body composition and life style. For example, heart rate typically falls with childhood age as heart size (e.g., left ventricular mass, stroke volume) increases relative to body size (Batterham et al., 1997; Dewey et al., 2008; de Simone et al., 1998; El-Sheikh, 2005; Fleming et al., 2011; Porges et al., 2011), while respiratory frequency also falls between birth and adolescence (El-Sheikh, 2005; Fleming et al., 2011; Porges et al., 2011; Williams & Lopes, 2002). However, studies examining the influence of childhood age on cardiac autonomic control in healthy children appear to be largely equivocal and at present this important topic has not been subject to review.

The physiological mechanisms regulating cardiac autonomic activity are complex and multi-factorial. Recent animal studies have identified a clear role for circulating pro-inflammatory cytokines in evoking increases in sympathetic activity (Helwig et al., 2008; Niijima et al., 1991), reducing cardiovagal baroreflex sensitivity (Takagishi et al., 2010) and reducing HRV (Fairchild et al., 2009). Notably, obesity is characterised by low grade inflammation (Rodríguez-Hernández et al., 2013) and both obesity and plasma markers of inflammation are associated with impairments in cardiac autonomic function in adults (Soares-Miranda et al., 2012; Thayer et al., 2010; Thiyagarajan et al., 2012). In contrast to the extensive work conducted in adult populations, the effect of weight status on HRV in children remains less well understood.

Given this background the purpose of this review is to determine how childhood age influences autonomic control of the heart as assessed using HRV analysis, and determine whether there is sufficient evidence to identify how this may be modified by weight status.

1.2 METHOD

The review protocol was carried out in accordance with the Centre for Reviews and Dissemination guidelines (2008).

1.2.1 Review question and inclusion criteria

This review has two main objectives:

Objective 1: Determine how childhood age influences HRV.

Objective 2: Determine whether there is sufficient evidence to identify how weight status and body composition affect HRV in children.

In accordance with the UN convention (UNICEF, 1989) a child was defined as an individual under the age of 18 years. Studies were included only if participants had no history or symptoms of cardiovascular, pulmonary, metabolic, or neurological disease and were not taking over the counter or prescribed medication. Studies assessing age were included if they compared children of different ages, whilst those which made comparisons between a group of children and a group of adults were excluded. Adults were excluded for the reason that the focus of the review was to understand how cardiac autonomic control changes explicitly throughout childhood. Only studies which employed an objective measure of weight status (e.g., body mass index [BMI], waist circumference) or a measure of body fat percentage (e.g., skinfold measures, dual-energy X-ray absorptiometry) were included.

Studies which assessed at least one indices of HRV measurement in accordance with the guidelines provided by the Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology (1996) were included. Both short-term (2-5 minutes) and long-term (24 hours) indices of HRV were used to provide an indication of overall HRV, and the components associated with cardiac parasympathetic or sympathetic activity. Assessments of overall HRV included SDNN (standard deviation of all RR [NN]

intervals), SDANN (standard deviation of 5 minute average RR interval over a 24 hour period), HRV triangular index (total number of NN intervals divided by the number of NN intervals in the modal bin of the NN interval histogram) and TINN (baseline width of the NN interval histogram measured as a base of a triangle). Cardiac parasympathetic activity was evaluated using RMSSD (square root of the mean of the sum of successive differences), pNN50% (proportion of RR intervals differing by >50 ms from previous RR interval) and power spectral density at the high frequency range (HF, 0.15–0.4Hz) (Malliani et al., 1991; Pagani et al., 1997; Task Force, 1996). Power spectral density at the low frequency range (LF, 0.04–0.15 Hz) was used as a composite index of cardiac sympathetic and parasympathetic activity (Malliani et al., 1991; Pagani et al., 1997; Task Force, 1996), and the LF:HF ratio used to provide an evaluation of the relative contribution of the sympathetic and parasympathetic components to the autonomic control of the heart rate (Pagani et al., 1997; Task Force, 1996). However, it is acknowledged that the use of ratio between LF and HF power spectral density as an estimate of so called 'sympathovagal balance' has been questioned, and that a satisfactory HRV derived index of cardiac sympathetic activity is lacking (Task Force, 1996 Taylor et al., 2006).

1.2.2 Search Strategy

Pubmed, Embase, and Cochrane Database of Systematic Reviews were searched for articles published from May 1966 to July 2014. The following search terms were used: heart rate variability, autonomic nervous system, autonomic control of the heart, cardiovascular autonomic function/control, aging, ageing, pre-school, children, child, adolescent, pre-pubertal young children, infants and obese. Searches were limited to those published in the English language to enable accurate interpretation of the results. A total of 8605 articles were identified. Following initial screening of titles and abstracts against the inclusion criteria 55

articles were identified and the full text screened in detail for eligibility by researchers (E.L.J.E, J.P.F and M.J.D). Disagreements were discussed with an advisor (S.B) and an additional 31 articles were excluded (Figure 1).

1.2.3 Data extraction

Data extraction records were made for each of the 24 studies eligible for inclusion. The author, aim, design, participant characteristics, indices used for the measurement of HRV analysis, conditions during measurement, reliability and validity, inclusion/exclusion, statistics and main findings were extracted (Table 1, Table A.1 & A.2).

1.2.4 Quality assessment

Each study was critically appraised and the quality assessed in accordance with the Centre for Reviews and Dissemination (2008). A quality index score (QIS) was given to each study according to the following criteria; participant characteristics, control group used (if applicable), control group appropriately matched, control/adjustments made for group differences, sample size, inclusion/exclusion criteria, technical approach to HRV measurement, study controls (e.g. respiratory rate, time of day, posture, physical activity, maturation). A graded score was given for each parameter (0 = not mentioned, 1 = mentioned, 2 = mentioned in detail). Variations in the aim and design of studies resulted in differences in the maximum possible scores. For example, in studies examining long-term HRV it is not possible to control for posture or breathing during the 24 hours of obtained measurement over daily living. To account for these differences a percentage score was calculated for each study in which the score achieved was divided by the maximum possible score, which was then multiplied by 100 (Table A.1 & A.2). Two reviewers (E.L.J.E and M.J.D) assessed the quality index score. Any disagreements were discussed until a consensus was reached.

1.3 RESULTS

1.3.1 Influence of childhood age on HRV

Seven case control studies examined the association between childhood age and HRV over a 24-hour period (Supplementary Table 1, QIS range 45-100%). Three employed correlation analyses to evaluate the relationship between childhood age and HRV as continuous variables (Massin & von Bernuth, 1997; Massin et al., 2000; Seppälä et al., 2014). The other four examined HRV in groups of children stratified according to age (Faulkner et al., 2003; Kazuma et al., 2002; Mitchels et al., 2013; Silvetti et al., 2001). Two of the seven case control studies reported mean RR interval, both showing an increase with childhood age (Massin & von Bernuth, 1997; Mitchels et al., 2013).

Massin and von Bernuth (1997) observed a notable increase in 24 hour SDNN from birth (full-term neonates) to infancy (12 months) which was followed by a steady increase throughout childhood (from 12 months to 15 years). Similarly, Silvetti et al (2001) identified a significant increase in SDNN from the youngest age group (1-5 years, n=23) to older age groups studied (6-10 years, n=28 and 11-15 years, n=37). However, no significant differences were observed between the older age groups (Silvetti et al., 2001). In the same study SDANN was reported to be significantly increased with childhood age (Silvetti et al., 2001). No association between short-term SDNN and age was observed in a large study of Finish children within a relatively narrow age range of 6 and 8 years (Seppälä et al., 2014) (Table 1).

Massin and von Bernuth (1997) observed a progressive increase in RMSSD and HF power from birth to 15 years. Similarly, Silvetti et al (2001) identified that RMSSD and pNN50% were significantly lower in children aged between 1-5 years, than groups of children aged 6-10 years and 11-15 years. In contrast, a significant negative association between age and HF power was found in children aged 6 – 8 years, but no associations were

found with RMSSD and pNN50% (Seppälä et al., 2014). In a study of male Japanese children, Kazuma et al., (2002) reported that HF power was not significantly different between groups with a mean age of 6.3 ± 0.5 (n=18), 8.7 ± 0.5 (n=14) and 10.9 ± 0.9 (n=38) years (mean ± SD) (Table 1).

Two studies examined LF power in children. Seppala et al. (2014) reported no association between LF power and age in children aged from 6 to 8 years, while Kazuma et al (2002) reported a significant increase in LF power in children aged between 6 to 11 years. Massin and von Bernuth (1997) identified that LF:HF ratio is highest at birth and markedly and progressively decreases to 12 months. Thereafter a slight reduction in LF:HF ratio was observed between early and late childhood. In contrast, in a study with a lower quality score index (QIS 45%), Kazuma et al. (2002) reported a significant increase in LF:HF ratio and LF power in children aged between 6 to 11 years, whereas Seppala et al. (2014) reported no association between childhood age and LF:HF ratio (Table 2).

1.3.1.1 HRV and circadian rhythm

Massin et al. (2000) reported that LF:HF ratio was higher during the day than at night in children >3 years, while overall HRV (SDNN) and RR interval were higher at night than day in children >2 years. In addition, RMSSD and HF power were observed to be higher at night in children >1 year, while pNN50% and LF power were higher at night in children >4 months. Similarly, Kazuma et al. (2002) showed that HF and LF were greater at night in children aged 6-11 years, whereas LF:HF ratio was higher during the day.

1.3.1.2 Age, sex and HRV

Four studies (Faulkner et al., 2003; Michels et al., 2013; Seppälä *et al*., 2014; Silvetti et al., 2001) meeting the inclusion criteria considered the influence sex and age on HRV in

children. Faulkner et al. (2003) suggested that adolescent girls (13-18 years) exhibit lower long-term overall HRV (SDNN, SDANN), cardiac parasympathetic activity (RMSSD, pNN50%, HF power) and LF power, compared to adolescent boys. Whereas, Silvetti et al (2001) reported that long-term SDNN and SDANN were lower in girls aged 1-15 years, boys and girls had similar RMSSD and pNN50% values. Neither study reported an interaction between childhood age and sex (Faulkner et al., 2003; Silvetti et al., 2001). In a methodologically rigorous study employing a large sample size of 460 children aged between 5-10 years, Michels et al. (2013) (QIS 100%) reported an interaction between childhood age and sex, such that short-term SDNN, RMSSD, pNN50, HF power (absolute units) and heart rate were generally higher in girls, except for between 5-6 years. Conversely, Seppälä *et al* (2014) reported no sex differences in HRV (SDNN, RMSSD, pNN50%, HF power, LF:HF ratio) in children aged 6 – 8 years (n= 465).

1.3.2 Childhood weight status, body composition and HRV

A total of 20 studies have examined the influence of weight status or body composition on short and long-term HRV (Table 2 & A.2). Of these studies, 11 examined the effect of weight status on heart rate in obese children (Altuncu et al., 2012; Baum et al., 2013; Birch et al., 2012; Kaufman et al., 2007; Martini et al., 2001; Nagai et al., 2003; Paschoal et al., 2009; Rabbia et al., 2003; Tonhajzerova et al., 2008; Vanderlei et al., 2010a, c). All of these studies reported a numerically higher heart rate and/or shorter RR interval in obese children, but these apparent differences only reached statistical significance in six studies (P<0.05) (heart rate; Altuncu et al., 2012; Martini et al., 2001; Nagai et al., 2003; Rabbia et al., 2003, RR interval; Martini et al., 2001; Tonhajzerova et al., 2008; Vanderlei et al., 2010a, Table 2)

Seven studies examined the influence of weight status on SDNN (Table 2 & A.2). Two of these studies assessed short-term HRV (Vanderlei et al., 2010a; Paschoal et al., 2009), with Vanderlei et al. (2010a) (QIS 73%) noting a reduction in SDNN in obese children (n=56) compared to age and sex matched children of ideal weight (n=61). A further five utilised long-term HRV assessments (Faulkner et al., 2003; Martini et al., 2001; Rabbia et al., 2003; Riva et al., 2001; Taşçılar et al., 2011) with three reporting no difference in SDNN between obese and ideal weight children (Faulkner et al., 2003; Martini et al., 2001; Taşçılar et al., 2011) (QIS range 36-65%) and two reporting lower SDNN values in obese children (Rabbia et al., 2003; Riva et al., 2001)(QIS range 32-50%). In the only study assessing physical activity, Rabbia et al. (2001) reported no differences between obese and control groups. SDANN was also reported in four of these studies with half reporting lower values in obese children (Riva et al., 2001; Taşçılar et al., 2011) (QIS 32-65%) and half reporting no difference (Martini et al., 2001; Rabbia et al., 2003) (QIS 36-50%). Some of these discrepancies may relate to; the unequal control groups with a tendency for the control group to be one year younger (Riva et al., 2001; Martini et al., 2001; Rabbia et al., 2003), failing to match for sex (Martini et al., 2001; Paschoal et al., 2009), and failing to consider resting heart rate (Faulkner et al., 2003; Paschoal et al., 2009; Riva et al., 2001; Taşçılar et al., 2011) or physical activity (Faulkner et al., 2003; Martini et al., 2001; Paschoal et al., 2009; Riva et al., 2001; Taşçılar et al., 2011; Vanderlei et al., 2010). Thus, there appears to be no clear consensus regarding the effects of childhood obesity on overall HRV on the basis of time domain measures. In contrast, geometric measures (HRV triangular index and TINN) of overall HRV are reduced in obese children (Taşçılar et al., 2011; Vanderlei et al., 2010c) (QIS 64-65%).

A total of 20 studies have assessed cardiac parasympathetic activity in groups of obese and normal weight children (Table 2 & A.2). The majority of these studies suggest that

RMSSD (8 of 13 studies, QIS range 32-73%), pNN50% (7 of 9 studies, quality score index range 32-73%) and HF power (14 of 18 studies, QIS range 36-73%) are lower in obese children compared to normal weight children. These findings are not contingent on whether short or long-term HRV analyses were undertaken. In the studies reporting no statistical differences in RMSSD and pNN50% values between obese and normal weight controls (Baum et al., 2013; Faulkner et al., 2003; Kaufman et al., 2007; Paschoal et al., 2009; Soares-Miranda et al., 2011) the sample size tended to be lower (range; 16-149 participants vs. 45-182 participants). In the two studies, which reported no weight-related differences in HF power when expressed as normalised units, differences between obese and normal weight children were observed when values were presented in absolute units (Vanderlei et al., 2010a, b). Four of these studies assessed the relationship between weight and long-term HRV in a cohort of children, with three showing significant negative correlations between weight status and RMSSD, pNN50% and HF power (Birch et al., 2012; Chen et al., 2012; Silvetti et al., 2001) (QIS range 42-56%). One excluded participants engaging in competitive sports (Silvetti et al., 2001) and another assessed physical activity by questionnaire (Chen et al., 2012). The latter reported a reduced physical activity in obese children and a positive correlation between physical activity and HRV when obese and non-obese groups were pooled (Chen et al., 2012). However, to what extent physical activity and weight status were independently associated with HRV was not determined. One study examined the relationship between weight and short-term HRV in a cohort of children, also reporting a significant negative correlation between weight status and ln(HF) (Baum et al., 2013) (QIS = 69%) and no difference in heart rate between groups.

A total of 18 studies assessed LF power in groups of obese and normal weight children (Table 2 & A.2). The majority of these studies reported no difference in LF power between obese and normal weight children (Altuncu et al., 2012; Birch et al., 2012; Faulkner

et al., 2003; Kazuma et al., 2002; Martini et al., 2001; Paschoal et al., 2009; Rabbia et al., 2003; Vanderlei et al.,2010a, b; Zhou et al., 2012) (10 of 18 studies, QIS range 36-73%). In one of these studies aerobic exercise capacity was determined and reportedly reduced in obese children (i.e., lower VO_2 peak) (Paschoal et al., 2009). A total of 15 studies have assessed LF:HF in groups of obese and normal weight children (Table 2 & A.2). The majority of these studies reported that LF:HF is increased in obese children (Altuncu et al., 2012; Birch et al., 2012; Kaufman et al., 2007; Kazuma et al., 2002; Martini et al., 2001; Paschoal et al., 2009; Rabbia et al., 2003; Riva et al., 2001; Soares-Miranda et al., 2011; Taşçılar et al., 2011) (10 of 15 studies, QIS range 32-65%). One of these studies assessed physical activity and reported no difference between groups (Rabbia et al., 2003). One study examined the relationship between weight and short-term HRV in a cohort of children, reporting no dependence of ln(LF) or LF:HF ratio on BMI (Baum et al., 2013).

1.4 DISCUSSION

1.4.1 Explanation of findings

The major findings of this literature review are threefold. First, the HRV changes in infancy (birth to ~12 months) are consistent with a marked and progressive increase in cardiac parasympathetic activity (increased RMSSD, HF power) relative to sympathetic activity (reduced LF:HF ratio). Second, during early-to-late childhood this trend appears to continue but at a reduced rate. Finally, a majority of studies reported that parasympathetic activity to the heart is reduced in obese children (reduced RMSSD, pNN50%, HF power), while 54% of studies reported that LF:HF ratio is increased suggestive of a relative heightening of cardiac sympathetic activity.

1.4.1.1 Influence of childhood age on HRV

There is a paucity of good quality studies examining cardiac autonomic control using HRV in infants (birth to 12 months). Only 1 study met the inclusion used in our review. This reported that 24 hour SDNN was increased while LF:HF was reduced from birth to 1 year, the latter being suggestive of an increase in cardiac parasympathetic activity relative to sympathetic activity. This pattern of autonomic development appears to continue more gradually during early childhood and more gradually still during late childhood. However, establishing the specific time course and nature of the change in cardiac autonomic function during childhood is challenging due the inconsistent methodological approaches adopted. For example, a limited number of studies (n=2) have evaluated childhood age as a continuous variable, while the others (n=4) have evaluated groups of children stratified according to age, often including only a handful of children and examining a relatively narrow age range. In a high quality study (QIS =100%), Michels et al (2013) assessed short-term HRV in a large sample of children (n=460) and identified an interaction between childhood age and sex on

cardiac autonomic function. While in girls a progressive increase in indices of cardiac parasympathetic activity (RMSSD, pNN50%, HF power) between 5 to 10 years, boys exhibited a 'wave like' pattern where these indices transient decline between 7 to 8 years. Further longitudinal studies are warranted to confirm the interactions between childhood age and sex on HRV.

There are a multitude of factors which may underlie the age related alterations in HRV described (e.g., heart rate, respiration, growth and maturation, hormones, arterial baroreflex, body composition, and life style). Heart size (e.g., left ventricular mass, stroke volume) (Batterham et al., 1997; Dewey et al., 2008; de Simone et al., 1998; Fleming et al., 2011) relative to body size is positively correlated with childhood age (Fleming et al., 2011; Porges et al., 2011; Winsley, 2006) and associated with this heart rate decreases, consequently the RR interval increases with age (Parati et al., 1995; Thiyagarajan et al., 2012). Respiratory frequency also declines from birth to adolescence and is reported to affect LF and HF power (El-Sheikh, 2005; Fleming et al., 2011; Porges et al., 2011; Williams & Lopes, 2002). Furthermore, children develop, grow and mature at different rates, and the age at which adiposity rebound and peak height velocity occur can vary, and is also modified by sex (Malina et al., 2004). Whether allometric scaling for body size (height, fat free mass) diminish childhood age-related differences in autonomic function, as it can in adults (Dewey et al., 2008; George et al., 1999; Urhausen et al., 1996) has not been examined. Sex hormones can modulate the central regulation of cardiac autonomic activity (El-Mas & Abdel-Rahman, 2009; Leicht et al., 2003), but the extent to which this may explain the sex and/or age differences in HRV reported in children is unknown. Only Michels et al. (2013) have evaluated how lifestyle factors may affect HRV in girls and boys. Cardiac parasympathetic activity (RMSSD, pNN50%, HF power) was observed to be strongly and positively associated with fitness (Eurofit fitness test battery (Council of Europe, 1993) , independent of

body composition, physical activity or heart rate, however only associated with objectively assessed physical activity (accelerometry) in boys and fat-free mass in girls (Michels et al., 2013).

1.4.1.2 Childhood weight status, body composition and HRV

Overall, the studies examined indicate that in obese children parasympathetic activity to the heart is reduced (RMSSD lower in 8 of 13 studies, pNN50% lower in 7 of 9 studies, HF power lower in 14 of 18 studies), while LF:HF ratio is increased in 67% of studies (elevated in 10 of 15 studies) suggestive of a relative increase in cardiac sympathetic activity. The mechanisms underlying such autonomic alterations remain inconclusive. Notably, elevated plasma concentrations of leptin, 8-isoprostane, and C - reactive protein and insulin resistance are associated with reductions in HRV derived indices of cardiac parasympathetic activity (e.g., HF power, RMSSD, pNN50%) in children; however when fat mass was adjusted for this relationship was no longer observed (Kaufman et al., 2007). Such findings indicate the importance of utilizing specific measures of adiposity (e.g., fat mass, fat free mass, percentage body fat), however the vast majority of studies examining the relationship between weight status and HRV have used BMI, which does not differentiate between fat mass vs. fat free mass or body fat distribution. Notably, elevated visceral adiposity but not BMI is associated with reductions in HRV derived indices of cardiac parasympathetic activity and increases in cardiac sympathetic activity in children (Soares-Miranda et al., 2011) and adults (Windham et al., 2012), perhaps because of the pro-inflammatory nature of visceral fat (Lapice et al., 2009). BMI also does not accurately predict adiposity at low to medium ranges (i.e., control groups) which may affect comparisons between normal and obese groups (Reilly, 2010). Collectively, these findings highlight the importance of using sophisticated approaches when evaluating the influence of weight status and body composition on cardiac

autonomic regulation in children. Finally, although age and sex specific BMI percentiles (Cole et al., 1998) were typically reported in the studies reviewed a marked heterogeneity in whether the national (>95th centile) or the clinical (>98th centile) cut off was used to identify an obese child, meaning that caution is required when comparing studies.

1.4.2 Limitations and future directions

To date no longitudinal study of childhood age and HRV has been published. Studies are required to better understand how impairments in HRV at childhood track into adulthood and whether they are associated with adult cardiovascular and metabolic health. Despite the present review taking a rigorous approach and including only those cross-sectional studies which adhered to published guidelines for assessing HRV (Task Force, 1996), a considerable heterogeneity in the approaches utilized was evident (e.g., HRV indices reported, body position used, control of breathing, laboratory based vs. field test evaluation) and generally small sample sizes used for age or weight sub-groupings. In addition, there are numerous physiological and life-style factors which can affect HRV which have not been consistently controlled or adjusted for in studies evaluating the influence of childhood age (e.g. sex, physical activity, puberty, Z scores for weight). Future research would benefit from more sophisticated assessment of body composition, as well as objective assessment (e.g. accelerometer) and statistical control for variations in physical activity. Ethnicity might also independently affect HRV in children (Eyre et al., 2013; Faulkner et al., 2003; Reed et al., 2006) but this remains to be fully elucidated. As mentioned above, the physiological correlates of HRV indices is debated and importantly a robust HRV derived assessment of cardiac sympathetic activity is lacking (Taylor et al., 2006; Task Force, 1996), albeit the use of LF:HF ratio has been widely use to estimate the relative contribution of cardiac sympathetic and parasympathetic control (Taylor et al., 2006; Task Force of the European

Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Furthermore, obtaining an artefact free, basal ECG recording in very young children is difficult and it is likely that movement and anxiety will influence the HRV assessment. In the present review we have focused on resting HRV, and future research is required to establish how cardiac autonomic responses to physiological stressors (e.g., exercise) are affected by childhood age and weight status. Despite the evidence that obesity has a deleterious influence on autonomic control of the heart in children the underlying mechanisms and extent to which this may be modified by life-style interventions (e.g., weight loss, increased physical activity) remains unclear. Finally, the review only includes published findings because of inherent difficulties in obtaining and comprehensively appraising investigations presented solely in abstract form (e.g., conference proceedings), thus a risk of publication and reporting bias is acknowledged.

1.4.3 Clinical Implications

Childhood obesity raises the risk of developing cardiovascular and metabolic disorders and is global public health issue. This review represents the first synthesis of studies evaluating the normal maturation of cardiac autonomic control using HRV analyses in healthy children, and indicates a marked and progressive increase in cardiac parasympathetic activity relative to sympathetic activity throughout childhood. Childhood obesity disrupts this normal development by attenuating cardiac parasympathetic activity, with some indication that sympathetic activity is also heightened. Such autonomic dysfunction has been associated with numerous deleterious physiological effects (Fisher et al., 2009), however the clinical significance of the appearance in early life of such disruptions in the neural regulation of the heart remain to be fully elucidated.

1.5 Conclusion

The available evidence indicates a marked and progressive increase in cardiac parasympathetic activity relative to sympathetic activity during infancy, which continues from infancy to late childhood albeit at a slower rate and a sex-specific profile. In obese children, reductions in cardiac parasympathetic activity and increases in sympathetic activity are indicated by a majority of studies, although the underlying mechanisms are unclear. The long-term significance of the deleterious childhood obesity-related changes in cardiac autonomic control to adult health and the extent to which these may be modified by life-style interventions remain to be fully determined.

Contributions

ELJE developed the original focus of the review, conducted the article search and quality assessments, and wrote original draft of the manuscript. MJD checked article eligibility and quality. JPF developed the original focus of the review, analysed the eligible articles and assisted with preparation of the manuscript. All reviewers approved the final version of the manuscript.

Acknowledgements

None.

Competing interests

No competing interests to declare.

Funding

ELJE was generously supported by the Department of Applied Science and Health, Coventry University, UK.

REFERENCES

Abboud, F.M., Harwani, S.C., Chapleau, M.W. (2012). Autonomic neural regulation of the immune system: implications for hypertension and cardiovascular disease. *Hypertension*, 59, 755-62. doi:10.1161/111.186833.

Altuncu, M.E., Baspinar, O., & Keskin, M. (2012). The use of short-term analysis of heart rate variability to assess autonomic function in obese children and its relationship with metabolic syndrome. *Cardiology Journal*, 19, 501-6.

Baum, P., Petroff, D., Classen, J., Kiess, W., & Blüher S. (2013). Dysfunction of autonomic nervous system in childhood obesity: a cross-sectional study. *PLoS One*, doi; 10.1371.005456.

Birch, S.L., Duncan, M.J., & Franklin, C. (2012). Overweight and reduced heart rate variability in British children: an exploratory study. *Preventive Medicine*, 55, 430-2. doi:10.1016/.2012.09.015.

Batterham, A.M., George, K.P., & Mullineaux, D.R. (1997). Allometric scaling of left ventricular mass by body dimensions in males and females. *Medicine and Science in Sports and Exercise*, 29,181-6.

Billman, G.E. (2006). A comprehensive review and analysis of 25 years of data from an in vivo canine model of sudden cardiac death: implications for future anti-arrhythmic drug development. *Pharmacology & Therapeutics*, 111, 808-35.

Centre for reviews and dissemination. (2008). Systematic reviews CRDS guidance for undertaking reviews in health care. York: CRD.

Chen, S.R., Chiu, H.W., Lee, Y.J., Sheen, T.C., & Jeng, C. (2012). Impact of pubertal development and physical activity on heart rate variability in overweight and obese children in Taiwan. *The Journal of School Nursing,* 28, 284-90. doi:10.1177/1059840511435248.

Cole, T.J., Freeman, J.V., & Preece, M.A. (1998). British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Statistics in Medicine*, 17, 407-29.

Council of Europe. (1988). Eurofit: Handbook for the EUROFIT tests of physical fitness. Rome: Commitee for the development of sport.

Eyre EL, Fisher JP, Smith EC, Wagenmakers AJ, & Matyka KA. (2013). Ethnicity and long-term heart rate variability in children. *Archives of Disease in Childhood,* 98, 292-8. doi:10.1136/2012-302266.

Dekker, J.M., Crow, R.S., Folsom, A.R., Hannan, P.J., Liao, D., Swenne, C.A., et al. (2000). Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: the ARIC Study. Atherosclerosis Risk in Communities. *Circulation,* 102,1239-44.

Dewey, F.E., Rosenthal, D., Murphy, D.J., Froelicher, V.F., & Ashley, E.A. (2008). Does size matter? Clinical applications of scaling cardiac size and function for body size. *Circulation*, 117, 2279-87.

de Simone, G., Devereux, R.B., Kimball, T.R., Mureddu, G.F., Roman, M.J., Contaldo, F., et al. (1998). Interaction between body size and cardiac workload: influence on left ventricular mass during body growth and adulthood. *Hypertension*, 31, 1077-82.
15.

El-Mas, M.M., & Abdel-Rahman, A.A. (2009). Longitudinal assessment of the effects of oestrogen on blood pressure and cardiovascular autonomic activity in female rats. *Clinical & Experimental Pharmacology & Physiology*, 36, 1002-9.doi:10.1111/j.1440-1681.2009.05192.

El-Sheikh, M. (2005). Stability of respiratory sinus arrhythmia in children and young adolescents: a longitudinal examination. *Developmental Psychobiology*, 46, 66-74.

Fairchild, K.D., Saucerman, J.J., Raynor, L.L., Sivak,J.A., Xiao, Y., Lake, D.E., et al. (2009). Endotoxin depresses heart rate variability in mice: cytokine and steroid effects. *American Journal of Physiology. Regulatory, Integrative & Comparative Physiology*, 297, R1019-27.doi:10.1152.00132.2009.

Faulkner, M.S., Hathaway, D., & Tolley, B. (2003). Cardiovascular autonomic function in healthy adolescents. *Heart & Lung*. 32, 10-22.

Fisher, J.P., Young, C.N., & Fadel, P.J. (2009). Central sympathetic overactivity: maladies and mechanisms. *Autonomic Neuroscience,* 148, 5-15.doi:10.1016.2009.02.003.

Fleming, S.,Thompson, M., Stevens, R., Heneghan, C., Plüddemann, A., Maconochie, I., et al. (2011). Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet,* 377, 1011-8. doi: 10.1016/SO140-6736(10)62226-X.

George, K.P., Gates, P.E., Whyte, G., Fenoglio, R.A., & Lea, R. (1999). Echocardiographic examination of cardiac structure and function in elite cross trained male and female Alpine skiers. *British Journal of Sports Medicine*, 33, 93-8.

Helwig, B.G., Craig, R.A., Fels, R.J., Blecha, F., & Kenney, M.J. (2008). Central nervous system administration of interleukin-6 produces splenic sympathoexcitation. *Autonomic Neuroscience*, 141,104-11.doi:10.1016/2008.04.008.

Kaufman, C.L., Kaiser, D.R., Steinberger, J., & Dengel, D.R. (2007). Relationships between heart rate variability, vascular function, and adiposity in children. *Clinical Autonomic Research*, 17, 165-71.

Kazuma, N., Otsuka, K., Wakamatsu, K., Shirase, E., & Matsuoka, I. (2002). Heart rate variability in normotensive healthy children with aging. *Clinical and Experimental Hypertension*, 24, 83-9.

Kleiger, R.E., Stein, P.K., & Bigger, J.T. (2005). Heart rate variability: measurement and clinical utility. *Annals of Noninvasive Electrocardiology,* 10, 88-101.

Lapice, E., Maione, S., Patti, L., Cipriano, P., Rivellese, A.A., Riccardi, G., et al. (2009). Abdominal adiposity is associated with elevated C-reactive protein independent of BMI in healthy non obese people. *Diabetes Care,* 32, 1734-6. doi:10.2337/dc09-0176.

Lammers, A.E., Munnery, E., Hislop, A.A., & Haworth, S.G. (2010). Heart rate variability predicts outcome in children with pulmonary arterial hypertension. *International Journal of Cardiology,* 142, 159-65. doi:10.1016.2008.12.087.

Leicht, A.S., Hirning, D.A., & Allen, G.D. (2003). Heart rate variability and endogenous sex hormones during the menstrual cycle in young women. *Experimental Physiology,* 88, 441-6.

Lown, B., & Verrier, R.L. (1976). Neural activity and ventricular fibrillation. *New England Journal of Medicine,* 294, 1165-70.

Malina,R.M., Bouchard, C., & Bar-or, O. (2004). *Growth and physical activity*. USA: Human Kinetics.

Malliani, A., Pagani, M., Lombardi, F., & Cerutti, S. (1991). Cardiovascular neural regulation explored in the frequency domain. *Circulation,* 84, 482-92.

Martini, G., Riva, P., Rabbia, F., Molini, V., Ferrero, G.B., Cerutti, F., et al. (2001). Heart rate variability in childhood obesity. *Clinical Autonomic Research,* 11,87-91.

Massin, M., & von Bernuth, G. (1997). Normal ranges of heart rate variability during infancy and childhood. *Pediatric Cardiology,* 18, 297-302.

Massin, M.M., Maeyns, K., Withofs, N., Ravet, F., & Gérard, P. (2000). Circadian rhythm of heart rate and heart rate variability. *Archives of Disease in Childhood,* 83, 179-82.

Michels, N., Clays, E., De Buyzere, M., Huybrechts, I., Marild, S., Vanaelst, B., et al. (2013). Determinants and reference values of short-term heart rate variability in children. *European Journal of Applied Physiology,* 113, 1477-88.doi:10.1007/s00421-012-2572-9.

Nagai, N., Matsumoto, T., Kita, H., & Moritani, T. (2003). Autonomic nervous system activity and the state and development of obesity in Japanese school children. *Obesity Research,* 11, 25-32.

Nguyen, N.T., Magno, C.P., Lane, K.T., Hinojosa, M.W., & Lane, J.S. (2008). Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. *Journal of the American College of Surgeons,* 207, 928-34.doi:10.1016/2008.08.022.

Niijima, A., Hori, T., Aou, S., & Oomura, Y. (1991). The effects of interleukin-1 beta on the activity of adrenal, splenic and renal sympathetic nerves in the rat. *Journal of the Autonomic Nervous System,* 36, 183-92.

Pagani, M., Montano, N., Porta, A., Malliani, A., Abboud, F.M., Birkett, C., et al. (1997). Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation,* 95(6):1441-8.

Parati, G., Saul, J.P., Di Rienzo, M., & Mancia, G. (1995). Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. *Hypertension,* 25, 1276-86.

Paschoal, M.A., Trevizan, P.F., & Scodeler, N.F. (2009). Heart rate variability, blood lipids and physical capacity of obese and non-obese children. *Arquivos Brasileiros de Cardiologia,* 93, 239-46.

Porges, S.W., & Furman, S.A. (2011). The Early Development of the Autonomic Nervous System Provides a Neural Platform for Social Behavior: A Polyvagal Perspective. *Infant and Child Development,* 20, 106-18.

Rabbia, F., Silke, B., Conterno, A., Grosso, T., De Vito, B., Rabbone, I., et al. (2003). Assessment of cardiac autonomic modulation during adolescent obesity. *Obesity Research,* 11, 541-8.

Reed, K.E., Warburton, D.E., Whitney, C.L., & McKay, H.A. (2006). Differences in heart rate variability between Asian and Caucasian children living in the same Canadian community. *Applied Physiology Nutrition and Metabolism,* 31, 277-82.

Reilly, J.J. (2010). Assessment of obesity in children and adolescents: synthesis of recent systematic reviews and clinical guidelines. *Journal of Human Nutrition and Dietetics,* 23, 205-11.doi:10.1111/j.1365-277x.2010.01054.x.

Riva P, Martini G, Rabbia F, Milan A, Paglieri C, Chiandussi L, et al. (2001). Obesity and autonomic function in adolescence. *Clinical and Experimental Hypertension,* 23(1-2):57-67.

Rodríguez-Hernández, H., Simental-Mendía, L.E., Rodríguez-Ramírez, G., & Reyes-Romero, M.A. (2013). Obesity and inflammation: epidemiology, risk factors, and markers of inflammation. *International Journal of Endocrinology*. doi: 10.1155/2013/678159.

Silvetti, M.S., Drago, F., & Ragonese, P. (2001). Heart rate variability in healthy children and adolescents is partially related to age and gender. *International Journal of Cardiology,* 81,169-74.

Seppälä, S., Laitinen, T., Tarvainen, M.P., Tompuri, T., Veijalainen, A., Savonen, K., et al. (2014). Normal values for heart rate variability parameters in children 6-8 years of age: the PANIC Study. *Clinical Physiology and Functioning Imaging,* 34, 290-6. doi:10.1111/cpf.12096.

Soares-Miranda, L., Alves, A.J., Vale, S., Aires, L., Santos, R., Oliveira, J., et al. (2011). Central fat influences cardiac autonomic function in obese and overweight girls. *Pediatric Cardiology,* 32, 924-8.doi:10.1007/s00246-011-0015-8.

Soares-Miranda, L., Negrao, C.E., Antunes-Correa, L.M., Nobre, T.S., Silva, P., Santos, R., et al. (2012).High levels of C-reactive protein are associated with reduced vagal modulation and low physical activity in young adults. *Scandinavian Journal of Medicine and Science in Sports,* 22, 278-84. doi:10.1111/j.1600.0838.2010.01163.x.

Takagishi, M., Waki, H., Bhuiyan, M.E., Gouraud, S.S., Kohsaka, A., Cui, H., et al. (2010). IL-6 microinjected in the nucleus tractus solitarii attenuates cardiac baroreceptor reflex function in rats. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, 298, R183-90. doi:10.1152/00176.2009.

Taşçılar, M.E., Yokuşoğlu, M., Boyraz, M., Baysan, O., Köz, C., & Dündaröz, R. (2011). Cardiac autonomic functions in obese children. *Journal of Clinical Research in Pediatric Endocrinology,* 3, 60-4.

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996). Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation,* 93, 1043-65.

Taylor,J.A., & Studinger, P. (2006). Counterpoint: cardiovascular variability is not an index of autonomic control of the circulation. *Journal of Applied Physiology,* 101, 678-81

Thiyagarajan R, Subramanian SK, Sampath N, Madanmohan Trakroo, Pal P, Bobby, Z. et al. (2012). Association between cardiac autonomic function, oxidative stress and inflammatory response in impaired fasting glucose subjects: cross-sectional study. *PLoS One*, doi: 10.1371.0041889.

Tonhajzerova, I., Javorka, M., Trunkvalterova, Z., Chroma, O., Javorkova, J., Lazarova, Z., et al. (2008). Cardio-respiratory interaction and autonomic dysfunction in obesity. *Journal of Physiology and Pharmacology*, 596:709-18.

Tsuji, H., Larson, M.G., Venditti, F.J., Manders, E.S., Evans, J.C., Feldman, C.L., et al. (1996). Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation,* 94, 2850-5.

Thayer, J.F., Yamamoto, S.S., & Brosschot, J.F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology,* 14, 122-31.doi:10.1016/2009.09.543.

Raitakari, O.T., Juonala, M., Kähönen, M., Taittonen, L., Laitinen, T., Mäki-Torkko, N., et al. (2003). Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Journal of American Medical Association,* 290, 2277-83.

Vanderlei, L.C., Pastre, C.M., Freitas, I.F., & Godoy, M.F. (2010a). Analysis of cardiac autonomic modulation in obese and eutrophic children. *Clinics (Sao Paulo),* 65, 789-92.

Vanderlei, L.C., Pastre, C.M., Freitas, I.F., & Godoy, M.F. (2010b). Geometric indexes of heart rate variability in obese and eutrophic children. *Arqvibos Brasileiros de Cardiologia,* 95, 35-40.

Vanderlei, L.C., Pastre, C.M., Freitas, I.F., & Godoy, M.F. 2010c. Fractal correlation of heart rate variability in obese children. *Autonomic Neuroscience,* 155, 125-9.

Whincup, P.H., Gilg, J.A., Papacosta, O., Seymour, C., Miller, G.J., Alberti, K.G., et al. (2002). Early evidence of ethnic differences in cardiovascular risk: cross sectional comparison of British South Asian and white children. *British Medical Journal,* 324, 635.

Windham, B.G., Fumagalli, S., Ble, A., Sollers, J.J., Thayer, J.F., Najjar, S.S., et al. (2012). The Relationship between Heart Rate Variability and Adiposity Differs for Central and Overall Adiposity. *Journal of Obesity.* doi: 10.1155/2012/149516.

Winsley, R.J. (2006). Cardiovascular function. In N. Armstrong (Eds.), *Paediatric Exercise Physiology*. (PP. 139-69). Oxford: Elsevier.

Williams, C.A., & Lopes, P. (2002). The influence of ventilatory control on heart rate variability in children. *Journal of Sports Science,* 20, 407-15.

World Health Organisation. (2010). Global recommendation on physical activity for health. Geneva: World Health Organisation.

UNICEF. (1989). The united nations convention on the rights of a child. London: UNICEF.

Urhausen, A., Monz, T., & Kindermann, W. (1996). Sports-specific adaptation of left ventricular muscle mass in athlete's heart. I. An echocardiographic study with combined

isometric and dynamic exercise trained athletes (male and female rowers). *International Journal of Sports Medicine,* 17, 3:145-51.

Zhou, Y., Xie, G., Wang, J., & Yang, S. (2012). Cardiovascular risk factors significantly correlate with autonomic nervous system activity in children. *Canadian Journal of Cardiology,* 28, 477-82.

Table 1: A summary of the influence of childhood age on HRV.

Age	HRV	References
Infancy (0-12 months)	• RR interval, SDNN, RMSSD and HF power lowest at birth. • LF:HF ratio highest at birth. • Marked and progressive increase in RR interval, SDNN, RMSSD, HF power, and decrease in LF:HF ratio, with age.	Massin & von Bernuth, 1997; Michels et al., 2013; Silvetti et al., 2001
Early to mid childhood (1-11 years)	• RR interval, SDNN, RMSSD, pNN50% and HF power higher than in infancy. • LF:HF ratio lower than in infancy. • RR interval, SDNN, RMSSD, pNN50% and HF power continues to increase, and LF:HF ratio continues to decrease, with childhood age albeit at a slower rate than during infancy.	Massin & von Bernuth, 1997; Michels et al., 2013; Silvetti et al., 2001
Late childhood (>11-18 years)	• RR interval, SDNN, SDANN, RMSSD, pNN50% and HF power highest. • LF:HF ratio lowest.	Massin & von Bernuth, 1997; Michels et al., 2013; Silvetti et al., 2001

HF - high frequency, **LF** - low frequency, **LF/HF** - the low frequency to high frequency ratio, **pNN50%** - proportion of RR intervals differing by >50 ms from previous RR interval, **RMSSD** - square root of the mean of the sum of successive differences, **SDANN** - standard deviation of 5 minute average RR interval over a 24 hour period, **SDNN** - standard deviation of all NN interval.

Table 2: Summary table of the number of studies on associations between measures of HRV and Weight

	HR	RR interval	SDNN	SDANN	Triangular index	TINN	RMSSD	pNN50%	HF	LF	LF:HF
Increased in obese	**4** (53: 36-73)									**5** (53:32-65)	**10** (49:32-65)
No difference	**3** (59: 46-69)	**3** (50: 42-63)	**4** (49: 38-65)	**2** (41: 36-50)			**5** (58:46-69)	**2** (48: 46-50)	**6** (51: 32-73)	**10** (52: 36-73)	**4** (65: 56-73)
Reduced in Obese		**3** (55:36-73)	**3** (52: 32-73)	**2** (49: 32-65)	**2** (65: 64-65)	**1** (64)	**8** (50: 32-73)	**7** (49: 32-73)	**14** (58: 36-73)	**5** (55: 58-73)	**1** (73)

Values are represented as the number of studies (mean quality index score: quality index score range)

HF - high frequency, **HR** – heart rate, **LF** - low frequency**, LF/HF -** the low frequency to high frequency ratio, **pNN50% -** proportion of RR intervals differing by >50 ms from previous RR interval, **QIS-** Quality index score, **RR –** beat to beat variability**, RMSSD** - square root of the mean of the sum of successive differences, **SDANN** - standard deviation of 5 minute average RR interval over a 24 hour period, **SDNN** - standard deviation of all NN intervals, **TINN** - triangular interpolation of NN interval histogram.

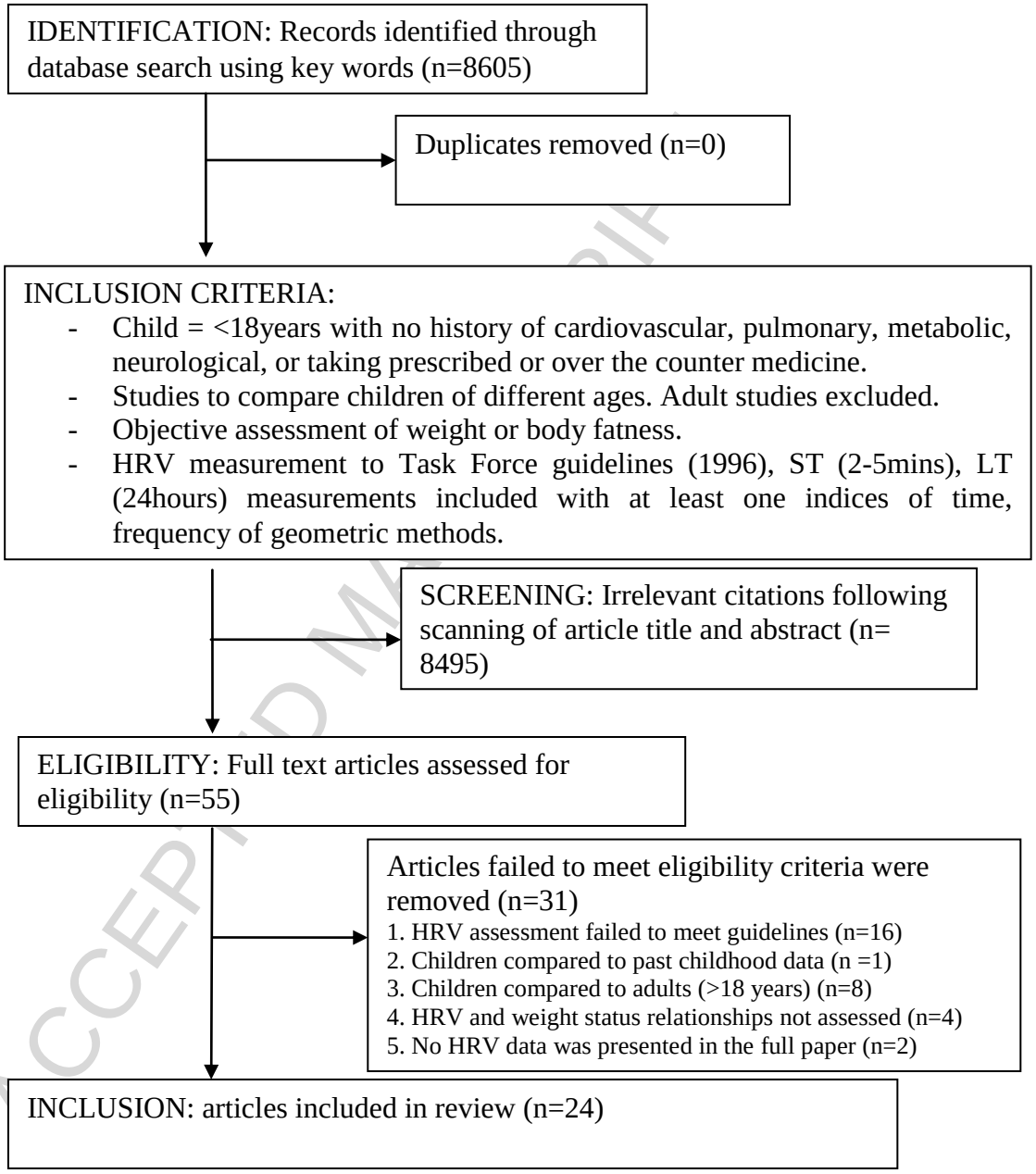


Figure 1 Flow chart outlining search strategy and selection process.

1.6 Appendices

Table A.1: Summary of case control studies assessing the relationship between childhood age and HRV

AUTHORS / STUDY AIM	PARTICIPANTS	HRV MEASUREMENT	EXPERIMENTAL CONDITIONS	RESULTS	QIS
Michels et al. (2013) To provide age- and sex-specific reference values for an extensive battery of ST HRV parameters and the contribution of age, sex, time point, body composition, physical activity and fitness.	460 healthy 240 male, 220 female 5-10yr 7% overweight **Group by age** 5yr (n=72), 6yr (n=62) 7yr (n=89), 8yr (n=113) 9yr (n=84), 10yr (n=40)	ST HRM (Polar Wearlink 31) **Analysis** Kubios Sampling frequency 1000Hz TD: RR interval, SDNN, pNN50%, RMSSD FD(FF): LF, HF, LF:HF ratio	**Reliability/validity** Manual checking **Inclusion/exclusion** CV disease, diabetes, and HRV too low quality (n=15) Registration cancelled if breathing was irregular. **Other** Breathing: normal Posture: Supine Body composition: BMI, BF% (BODPOD). No strenuous PA on measurement day. Fitness: Eurofit fitness test battery. PA: accelerometer HR and RR interval raw values reported.	**Statistics** t-test (sex) Two way ANOVA (sex/age) LMS Method (percentiles) **Age, sex & HRV** Correlation: Age positively correlated with TD (SDNN, pNN50%, RMSSD), FD (LF, HF, LF:HF ratio) and RR interval in boys and girls. HR higher in girls. ANOVA: Main sex effect: SDNN, RMSSD, pNN50%, LF and HF were higher in boys. Main age effect (increase with age) on SDNN, RMSSD, pNN50% and HF but not LF. Age and sex interaction found for SDNN, RMSSD, pNN50% and HF, showing higher values in boys at 5 and 6yr but no sex difference at older ages. Polynomial ANOVA: Cubic trend for bots in all HRV variables (sex and age interaction significant). Age and sex percentile curves provided. Multiple regression: age, PA, fitness and fat free mass predict HRV parameters.	100%

Massin & von Bernuth (1997) To assess HRV in infants, toddlers and school children during 24 hr ECG and to determine differences in variability as a function of age and mean RR interval over length of analysis.	210 healthy 108 male, 102 female **Group by age** 3-14yr (3-7days, 8-14days, 15-21days, 22days-1month, 1-3month, 3-6month and each yr following)	LT (NDA) ECG (2 channel) **Analysis** Sampling frequency 350Hz. Holter tapes & medilog for QRS detection TD: RR interval, SDNN, pNN50%, RMSSD. FD(FF): HF, LF:HF ratio	**Reliability/validity** Manual checking and edited to validate QRS labelling **Inclusion/exclusion** 23 hours, noise/ectopic files were rejected Medical history/physical examination. No disease. **Other** PA not assessed or reported RR interval values reported.	**Statistics** Linear/non linear regression models (HRV with age). **Age & HRV** Positive correlation between age and RR interval, SDNN, pNN50%, RMSSD and HF. LF:HF was highest at birth and evidenced a steadying during childhood. Independent effect of RR interval and age on HRV parameters.	60%
Seppä lä et al. (2014) To define reference values for the time- and frequency-domain measures of HRV.	465 healthy 239 male, 226 female 6-8yr	ST ECG (12 lead) **Analysis:** Sampling frequency 500Hz. Kubios TD: RR interval, HR, SDNN, pNN50%, RMSSD, HRV triangular index, TINN FD (FF): HF, LF:HF ratio.	**Reliability/validity** QRS detection algorithm Ectopic and erroneous beats were corrected using interpolation methods. RR series transformed using 4-Hz cubic spline interpolation **Inclusion/exclusion** Very low frequency removed **Other** Position: supine. PA not assessed or reported. HR and RR interval values reported for 6–8yr.	**Statistics** Mann-Whitney U –test (gender) Pearson correlation (age) **Age and HRV** Age negative significant association with HF. No association between age and all other HRV indices. Mean RR interval at 6-8yr = 72.5 and HR = 83.5bpm. **Gender and HRV** No significant gender differences between any HRV indices.	60%
Massin et al. (2000) To examine circadian variation in heart rate and	57 healthy 28 male, 29 female **Group by age** 2month -15yr (3 subjects per	LT (NDA) ECG (2 channel) **Analysis** Sampling frequency	**Reliability/validity** Manual checking and edited to validate QRS labelling **Inclusion/exclusion**	**Statistics** Mean hourly value for each parameter **Age & HRV** Circadian variation during childhood.	55%

HRV in children	group 2, 3, 4, 8month and then each yr after)	350Hz. Holter tapes & medilog for QRS detection TD: RR interval, SDNN, pNN50%, RMSSD. FD(FF): LF, HF, LF:HF ratio	24 hours 5 complexes classified as ectopic or noise per hr were rejected. No known disease, medication or abnormal rhythm **Other** PA not assessed or reported RR interval values reported.	LF:HF ratio increased in day and decreased at night from >3 yr. SDNN (from >2 yr) , RR interval, RMSSD, HF (from <1 yr), pNN50% and LF (4month) increased during the night and decreased during the day. Circadium variation disappears in very young due to fall in LF:HF and rise in other HRV due to daytime sleep episodes.	
Faulkner et al. (2003) To determine the effects of age, sex, race, BMI & tanner on ST CV tests & 24 hour HRV.	75 healthy adolescents 49 female, 26 male 14 African American 61 White **Age** 15.0±1.6 (13-18yr)	LT ECG **Analysis** Holter monitoring TD: SDNN, SDANN, pNN50%, RMSSD FD (FF): LF, HF	**Reliability/validity** QRS identified & labelled manually and edited for errors performed. Reliability/validity studies and reliability for short periods (3-65days) reported. **Inclusion/exclusion** Disease: acute, chronic illness excluded. 128 samples **Other** No food, drink or smoking 30mins before test, Temperature controlled PA not assessed or reported. HR and RR interval raw values not reported.	**Statistics** Correlation Two-way ANOVA (age/sex) **Sex, age & HRV** Boys significantly increase SDNN and SDANN than girls (early adolescence) ($P<0.05$). No other significant difference in LF, HF, pNN50% and RMSSD (age & sex)	50%

Silvetti et al. (2001) To define the values of 24hr HRV in normal children, adolescent divided by age/gender.	103 healthy 57 male, 46 female **Group by age** 1-20yr (1-5yr, 6-10yr, 11-15yr, 16-20yr)	LT ECG **Analysis** Holter monitoring Medilog excel (analyse) TD: SDNN, SDANN, RMSSD, pNN50%, mean HR.	**Reliability/validity** Tapes scanned by cardiologist, QRS identified, **Inclusion/exclusion** <20hr Significant artefacts higher than 200 isolated premature atrial, ventricular beats or pauses longer than 2s. Artefacts, ectopic, normal beats recognised and classified by template-matching techniques. No drugs or history of syncope. Participants engaging in competitive sports excluded. **Other** HR and RR interval raw values not reported.	**Statistics** Normality Two way ANOVA & interaction (age/sex), Bonferroni **Age & HRV** Mean RR interval increases with age ($P<0.0001$). SDNN increase in (1-5yr) compared to 6-10yr and 11-15yr ($P<0.05$). SDNN, SDANN positively correlate with increasing age and male sex. RMSSD significant lower in 1-5yr compared to 6-10yr and 11-15yr ($P<0.05$). pNN50% was significant reduced in 1-5yr compared to 6-10yr and 11-15yr ($P<0.05$).	50%
Kazuma et al. (2002) Examine relationship between HRV & childhood age	70 healthy (male only) Japanese 12 obese, 53 normal, 5 thin (obese over 20%, normal 10-20%, under (>10%). **Group by age** 6-12 yr (group 1: 6-7yr, n=18, group 2: 8-9yr, n=14, group 3: 10-12yr, n=38).	LT (24hrs) ECG **Analysis** Holter monitoring FD (FF): TP:0.01-0.05, LF:0.04-0.15, HF:0.15-0.4.	**Reliability/validity** RR not equal so used cardiac curve using 3 % curve spline, instantaneous RR at 125ms & reconstruct each RR series of 512S. Hanning windowing function to measure spectral leakage **Inclusion/exclusion** If premature supraventricular premature contraction shorter than 80% of proceeding contraction. No history of CV disease, hypertension, or other medical problems.	**Statistics** One way ANOVA, Krustal Wallis Test **Age & HRV** 24hr: TF, LF, LF: HF ratio increases with age. No difference in HF with age. Wake: TF, LF, HF increases with age. LF:HF was not significantly difference with age. Sleep: LF, LF: HF significantly increases with age. No significant difference in HF with age. .	45%

	Other PA not assessed or reported. HR and RR interval values not reported.

CV- cardiovascular, **ECG** – electrocardiogram, **FD** - frequency domain, **FF** - fast Fourier transform, **HF** - high frequency power, **HRV**- heart rate variability, **hr** – hour, **yr** – years, **LF** - low frequency power,

LF:HF - low frequency to high frequency ratio, **LT** - long term, **NDA** - normal daily activity, **PA** - physical activity, **S** – seconds, **ST**- short term, **TD** - time domain, **TP** - total power.

Table A.2: Summary of studies assessing the relationship between weight and HRV

AUTHOR/ STUDY AIM	PARTICIPANTS	HRV MEASUREMENT	EXPERIMENTAL CONDITIONS	RESULTS	QIS
Vanderlei et al. (2010a) To compare the autonomic function of obese and eutrophic children by analysing HRV. Case Control	121 children 57 male, 64 female 8-12yr **Group by weight** BMI: Cole et al.,(2000) age and sex cut off 56 obese 61 ideal (matched age and sex)	ST HRM (Polar S810i) **Analysis** Sampling frequency of 1000Hz, 1000 consecutive RR intervals Kubios TD: RR, RMSSD, SDNN, pNN50% FD (FF): LF, HF, LF/HF. Poincare plot: SD1, SD2, SD1/SD2 ratio	**Reliability/validity** Provides reference to paper for validity of HRM. **Inclusion/exclusion** Digital filtering (premature ectopic heartbeat & artefacts). 5% error in R-R series excluded (14 children) No drug/diagnosed disease 95% sinus rhythm included. **Other** Posture: dorsal prone Breathing: spontaneous Temperature controlled PA not assessed or reported RR interval values reported.	**Statistics** Normality t-test, Mann Whitney U test **Weight & HRV** TD: reduced RR interval, SDNN, RMSSD, pNN50% in obese compared to lean. FD: LF & HF (ms^2) significantly reduced in obese compared to lean (LF 250 ± 178 vs. 375 ± 213, HF 195 ± 183 vs. 249 ± 160, P<0.01). No significant difference in LF (NU), HF (NU), or LF:HF ratio. Poincare plot: reduced SD1, SD2 in obese. No difference in SD1/SD2 ratio.	73%
Nagai et al. (2003) To evaluate whether sympathetic and/or parasympathetic nerve activities were altered in an obese population. Case control	84 children 36 male, 48 female 9 ± 0.3yr Japanese **Group by weight** BMI 42 obese (obese BMI>120%: 18 male, 24 female) 42 non obese (18 male, 24 female)	ST ECG **Analysis:** Sampling frequency 1024Hz On a 256s time series TD: HR FD (FF): LF, HF	**Reliability/validity** Visual inspection **Inclusion/exclusion** Linear trend & direct currency component were eliminated by digital filtering between 0.02 – 0.05. Disease: medical history, no drugs or disease. **Other**	**Statistics** t-test Partial correlation **Weight & HRV** TD: Higher resting heart rate in obese than non-obese (90.7 vs. 84.3bpm, P <0.001). FD: All components were significantly lower in obese group than non-obese (LF 6.16 ± 0.12 vs. 6.42 ± 0.05, P<0.05, HF 5.84 ± 0.15 vs. 6.34 ± 0.07, P<0.01). LF:HF	73%

			Posture: seated chair Breathing: normal breathing Temperature controlled. PA: health questionnaire HR values reported.	ratio in obese was negatively correlated to duration of obesity. Reduced LF, HF in >3 years compared to <3years. **Other** None of the children engaged in sport or aerobic exercise.	
Baum et al. (2013) To assess the distribution of ANS dysfunction in overweight and obese children. Cross sectional	149 children 12.0yr **Group by weight** BMI 90 Overweight/obese (BMI>97th: 45 male 45female) 59 Normal weight (BMI 10-90th, 34 male, 25 female) German reference values	ST **Analysis:** TD: HR, RMSSD FD (FF): LF, HF, LF:HF ratio	**Reliability/validity** NR **Inclusion/exclusion** Disease: medical history and physical examination **Other** Posture: resting positiom Breathing: deep breathing 6 cycles per minute PA not assessed or reported. HR values reported.	**Statistics** Linear model Two sample t-test **Weight & HRV** TD: HR not significantly different between obese and normal weight. RMSSD no significant dependence on BMI. FD: ln(HF) was significantly related to BMI, age and gender which explained a large proportion or variance. Ln(HF) was lower in obese than normal weight. LF:HF ratio was not significantly related to BMI (P=0.05).	69%
Taşç ilar et al. (2011) To evaluate the autonomic system by measuring HRV in obese Case control	62 children 39 male, 23 female 11.6 ± 2.0yr **Group by weight status** BMI greater than 97th centile age & sex and below 85th for controls (IOTF) 32 obese (20 male, 12 female) 30 healthy (age and sex matched, 19 male, 11 female)	LT (NDA) ECG **Analysis** Holter Sampling frequency1024Hz TD: SDANN, SDNN, RMSSD, pNN50% , HRV triangular index, FD (PSA): LF, HF, LF:HF ratio	**Reliability/validity** NR **Inclusion/exclusion** Medical history and examination Disease **Other** PA not assessed or reported. HR values not reported.	**Statistics** t-test (non obese vs. obese) Mann Whitney U test Chi square **Weight & HRV** TD: No difference in SDNN. SDANN (obese 102 ± 25 vs. normal 122 ± 22ms, P<0.001), RMSSD (obese 73 ± 37 vs. normal 89 ± 45, P<0.001), pNN50% (obese 27 ± 16 vs. normal 34 ± 13, P<0.001) lower in obese. HRV (triangular index) (obese 40 ± 1.1 vs. normal 48 ± 12, P<0.009).	65%

				FD: HF (NU) (obese 1.9 ± 1.5 vs. normal 2.5 ± 2.1 P=0.03) significantly reduced in obese. LF (obese 2.6±0.9 vs. normal 2.2 ± 1, P=0.014) and LF:HF ratio (obese 1.6 ±0.7 vs. normal 1.12 ± 0.56, P=0.007) significantly higher in obese compared to controls.	
Vanderlei et al. (2010b) To investigate the autonomic modulation of eutrophic and obese children by means of indexes of HRV obtained by geometric methods. Case control	133 children 63 male, 70 female 8-13yr **Group by weight** BMI: Cole et al.,(2000) age and sex cut off 61 obese (28 male, 33 female, 10.2 ± 1.47yr) 72 normal (35 male & 37 female, 10.57 ± 1.51yr)	ST HR monitor (polar S810i) **Analysis** Sampling frequency 1000Hz, used 1000 consecutive R-R intervals. Geometric methods: RRtri, TINN Poincare plot: SD1, SD2, SD1/SD2 ratio.	**Reliability/validity** Referred to validity of polar for beat to beat. Digital filtering & manual filtering. **Inclusion/exclusion** Eliminate premature , artefacts & ectopic beats No medication infections, metabolic or cardio-respiratory diseases. **Other** Posture: supine Breathing: spontaneous breathing Temperature controlled PA not assessed or reported. HR values not reported.	**Statistics** Normality t-test, Mann Whitney U test **Weight & HRV** Geometric: RRtri (0.073 ± 0.02 vs. 0.1084 ± 0.13, P =0.000), TINN (171.8 ± 55.1 vs. 218. 2 ± 51.1, P = 0.008) were reduced in obese. Poincare plot: SD1(19.9 ± 9.10 vs. 24.1 ± 8.03, P= 0.006) SD2 (51.6 ± 16.5 vs. .8 ± 17. 2, P=0.000) were significantly lower in obese than normal (P<0.01). No significant difference in SD1/SD2 ratio.	64%
Vanderlei et al. (2010c) To analyse the HR dynamics in obese children by measuring short long term fractal components of HRV. Case control	112 children 53 male, 59 female 8-12yr **Group by weight** BMI Cole et al., (2000) age and sex cut off 51 Obese (23 male, 28 female) 61 non obese (30 male, 31	ST HR monitor (polar s810i) beat to beat **Analysis:** Sampling frequency 1000Hz. Fractal analysis applied to time series of R-R.	**Reliability/validity:** Digital filtering completed with manual to eliminate ectopic & artefacts **Inclusion/exclusion** 95% consecutive RR series. (1000 intervals used) **Other**	**Statistics** Normality t-test, Mann Whitney U test **Weight & HRV** FD: LF (ms^2) (260 ± 183 vs. 384 ± 212, P=0.001), HF (ms^2) (207 ± 186 vs. 252 ± 155, P=0.019) significantly reduced in obese. HR, LF, HF (NU) & LF: HF ratio showed no differences between obese and	63%

	female)	TD: HR FD (FF): LF, HF, LF: HF ratio	Posture: dorsal at rest Breathing: spontaneous Temperature controlled PA not reported HR reported	non obese. **Weight, Sex & HRV** LF (ms^2) significantly reduced in obese, girls than non obese girls. LF:HF ratio no significant difference.	
Kaufman et al. (2007) Cardiovascular autonomic (CANS) function and its potential relationship with leptin resistance. Case control	36 children 18 male, 18 female 11.5 ± 0.8yr Maturity: tanner stage 1.9 ± 0.8 **Group by weight** BMI (age adjusted) 10 normal (<85th centile: 6 male, 4 female) 10 overweight (>85th centile but >95th centile: 6 male, 4 female) 16 obese (>95th obese: 6 male, 10 female)	ST ECG (3 lead) **Analysis** 500Hz sample Metlab TD: RR interval, RMSSD FD (FF): LF, HF, LF:HF ratio.	**Reliability/validity:** Manually reviewed ectopic beats. Reproducibility data from lab reported mean difference 0.01±0.2 or SDRR. **Inclusion/exclusion** Disease: non diabetic but obese, duration of obesity also determined. Absence of diseases which affected CV function, orthostatic intolerance, syncopal episodes. Medical history and rest ECG before testing **Other** Posture: supine Breathing: no constraints Skin preparation, 10hr overnight PA not assessed or reported. RR interval values reported.	**Statistics** ANOVA (bonferroni) comparison between normal, overweight & obese. Transformed data - log (LF, HF (NU)). **Weight & HRV** TD: No difference in RR interval or RMSSD between obese and normal. FD: LF (NU) and LF:HF ratio higher in obese than controls (58.2 ± 11.8 vs 39.9 ± 10, P=0.001, 1.60 ± 0.84 vs. 0.70 ± 0.25, P=0.003), HF (NU) lower in obese than controls (41.8 ±11.8 vs. 60.1 ± 10, P=0.001).	63%
Soares- Miranda et al. (2011) To analyse the relationship between central adiposity and CANS function by HRV	16 overweight/obese (>85th 95th age and sex). Female only 8-16yr **Group by weight** DEXA	ST Polar HRM **Analysis** Polar precision Kubios	**Reliability/validity** NR **Inclusion/exclusion** **Other** Posture: supine	**Statistics** Normality ANCOVA (adjust for age. Tanner, total body fat) **Weight & HRV** TD: RMSSD was not significantly different	61%

in overweight & obese. Case control	8 Central fat above mean value 50 8 central fat below mean value 50.	TD: RMSSD FD (FF): LF, HF (ms & NU), LF:HF ratio	Breathing no constraints No drinks, 5-6pm, standardised conditions, quiet, nurse for testing. Avoid strenuous exercise HR values not reported.	between central fat above or below 50th centile. FD: LF (NU) and LF:HF ratio higher in central fat above 50th percentile (P=0.018, P=0.019) than under 50th percentile. HF (NU) lower in central fat above 50th centile than below (P=0.019). HF (ms^2) lower and LF (ms^2) higher in central fat above 50th percentile than below 50th percentile P=0.006).	
Chen et al. (2012) To explore the influence of puberty on autonomic development Case control	171 children 9-13yr **Group by weight** BMI 84 overweight/obese (44 male, 40 female) 87 normal (44 male, 43 female)	ST ECG (3 lead) Analysis Frequency 500Hz FD (FF): HF, LF	**Reliability/validity** Manual inspection and digitised **Inclusion/exclusion** Disease **Other** Breathing : normal Temperature Exercise (PA questionnaire and pubertal questionnaire). Avoid vigorous exercise and caffeine 2hr before testing. HR values not reported.	**Statistics** t-test (group/HRV) regression (PA, maturation and HRV) **Weight & HRV** LF and HF (ms^2) is significantly lower in overweight or obese compared to control (LF:5.9 ± 0.9 vs. 6.3 ± 0.8, P<0.05, HF 5.6 ± 1.3 vs. 6.3 ± 1.1). **Weight, puberty & HRV** No difference in puberty and HRV in control group. In obese group, LF and HF (Log) was significantly reduced in puberty group compared to prepuberty (P<0.05). No differences in puberty and post puberty group. **Physical activity, weight, puberty and HRV** Positive relationship between PA and HRV in pubertal obese group. Obese less active than control (P=0.01)	58%
Zhou et al. (2012)	180 children 100 Male, 80 Female	LT ECG	**Reliability/validity** NR	**Statistics** Normal	56%

To clarify whether multiple risk factors damage modulation in ANS in children. Cross sectional	10 ± 1.2yr **Grouped by weight** BMI	**Analysis** TD: SDNN, SDANN, RMSSD FD: LF, HF, LF:HF ratio.	**Inclusion/exclusion** Healthy (health questionnaire) Pre existing arrhythmia. No drugs or disease **Other** 24hr avoid strenuous exercise & stimulant foods. Avoid TV computer for 24 before ECG. HR values not reported	Multiple regression **Weight &HRV** BMI & WC correlated negatively with RMSSD & HF. **HRV & CV factors** Reduced SDNN, RMSSD, LF, HF with increased risk factors	
Tonhajzerova *et al* (71) To examine whether evaluation of the cardio-respiratory interaction using different methods-the heart rate and BP variables analysis & respiratory manoeuvres can reveal early subclinical autonomic dysfunction in obese adolescents Case control	40 children 16 male, 24 female 12-18yr **Group by weight** BMI (IOTF) 20 obese (8 male, 12 female, 14.8±0.5yr) 20 healthy- matched by age & gender.	ST ECG **Analysis** Sample frequency 500Hz TD: RR interval. FD: HF	**Reliability/validity** Software detection for RR waves (500Mz time series) **Inclusion/exclusion** **No drugs or disease.** **Other** Posture: supine Breathing: no control PA not assessed or reported. RR values reported	**Statistics** Mann Whitney U test Unpaired t-test **Weight & HRV** TD: RR interval significantly shorter in obese (805 ± 17 vs. 939 ± 27, P=0.001). FD: HF significantly reduced in obese (P=0.043).	55%
Altuncu et al. *(*2012) Investigate MS parameters and CV autonomic system alteration in ANS and effectiveness of ST HRV to reveal CAD risk factors in early period in obese children. Case control	106 children 51 male, 55 female 8-16yr **Group by weight** BMI 66 obese (95th centile) 31male, 35 female 40 healthy control (20 male, 20 female)	ST ECG **Analysis** Holter TD: HR FD (FF, 250ms): LF, HF, (ms & NU), LF: HF ratio.	**Reliability/validity** Measurement manually revised by one operator. **Inclusion/exclusion** Ectopic beats which were deleted and removed from RR sequence. disease: medical history & physical examination no drugs or metabolic disease	**Statistics** t-test **Weight & HRV** TD: HR higher in obese (95.3bpm) than normal (77.5bpm, P<0.001). FD: No significant difference in LF between obese and control. HF was significantly lower in obese group than control group (obese 16 ± 13nu vs. 21 ± 14, P=0.046). LF:HF ratio significantly higher	54%

			Other Posture: sitting rest PA not assessed or reported. HR values reported.	in obese compared to control (3.8±2.3 vs. 2.3±0.9, P<0.01).	
Rabbia et al. (2003) To investigate CV autonomic function in pediatric obesity of different durations using time-domain, spectral, no linear methods Case control	62 children 13.9 ± 1.7yr (obese) & 12.9 ± 1.6yr (control) **Group by weight** BMI 50 obese (BMI: 97th centile), 12 Lean – sex matched. Recent obese (<4yr), Intermediate obese (4-7yr) long term obese (>7yr)	LT ECG Sampling frequency rate 300Hz **Analysis** Holter TD: HR, RR interval, SDNN, SDANN, pNN50%, RMSSD FD (FF): HF, LF (ms & NU), LF: HF ratio.	**Reliability/validity** Premature ventricular complexes, adjacent R-R intervals and noise were rejected by holter software. **Inclusion/exclusion** NR **Other** PA recorded as weekly hours in sport or play. HR values reported.	**Statistics** Spearman's rank (duration of obesity & HRV) Correct for height and left ventricular mass **Weight & HRV** TD: HR (day & night) higher in all 3 obese groups than control (P=0.001). SDNN, rMSSD, pNN50% (day & night) lower in obese groups compared to normal. No difference between obese and normal for SDANN and RR interval. FD: HF (NU) reduced and LF:HF ratio increased in obese than controls. No difference for LF(NU or ms). **Other** No difference in PA between obese and non-obese groups (P= 0.63).	50%
Faulkner et al. (2003) To determine the effects of age, sex, race, BMI & tanner on ST CV tests & 24 hour HRV. Cross sectional	75 healthy adolescents 15.0 ± 1.6 (13-18yr) 49 female, 26 male 14 African American 61 White **Weight** BMI	LT ECG **Analysis** Holter TD: SDNN, SDANN, pNN50%, RMSSD FD (FF): LF, HF	**Reliability/validity** QRS identified & labelled manually and edited for errors performed. Reliability/validity studies and reliability for short periods (3-65days) reported. **Inclusion/exclusion** Disease: acute, chronic illness excluded. 128 samples	***Statistics*** Correlation **Weight & HRV** No correlation between BMI & autonomic measures.	50%

			Other No food, drink or smoking 30mins before test, Temperature: 25-27 degree C. PA not assessed or reported. HR values not reported.		
Silvetti et al. (2001) To define the values of 2h HRV in normal children, adolescent divided by age/gender. Cross sectional	103 children 57 male, 46 female 1-20yr **Weight** BMI	LT ECG **Analysis** Holter Medilog excel (analyse) TD: RMSSD, pNN50%,	**Reliability/validity** Tapes scanned by cardiologist, QRS identified, **Inclusion/exclusion** ECG shorter than 20h. Artefacts, premature atria and ventricular beats or pauses removed Artefacts, ectopic, and normal beats recognised and classified by template-matching techniques. No drugs or history of syncope. Participants engaging in competitive sports excluded **Other** HR values not reported	**Statistics** Normality Correlation **Weight & HRV** BMI Significantly associated with pNN50% & RMSSD (Adjusted for sex & age)	50%
Paschoal et al. (2009) Effect if obesity in HRV, blood lipid & physical capacity of obese children. Case control	30 children 15 male, 15 female 9-11yr (9.8 ± 0.7) **Group by weight** BMI 15 obese (95th-97th centile, 8boys, 7girls) 15 non obese (5-85th centile,	ST Polar S810i **Analysis** Polar precision TD: HR,RR interval, SDNN, RMSSD, pNN50%	**Reliability/validity** NR **Inclusion/exclusion** No medication that could interfere **Other** Posture: supine (12min) & standing (7 min).	**Statistics** t-test or Mann Whitney U test Supine: No difference in obese vs. non obese. HR and RR interval not significantly different between obese groups. Obese vs. non obese standing	46%

	7boys, 8girls)	FD (FF): LF, HF(ms & NU), LF:HF ratio	no stimulants 8hrs sleep. Temperature controlled No sports 24hr prior or 2months prior. PA: parental interview Fitness: progressive exercise test. HR and RR interval values reported.	LF (NU) (0.71 ± 13.8 vs. 56.3 ± 18.8) and LF:HF ratio (3.8 ± 3.9 vs. 1.7 ± 0.9, P<0.05) was significantly higher in obese. No difference in SDNN, RMSSD, PNN50%, LF, HF (ms^2 and NU). Supine vs. standing for obese Increases in HRV in supine for obese (mean RR, SDNN, RMSSD, pNN50% (P<0.05). LF, HF (ms^2 & NU) significant higher in obese. **Other** Obese lower fitness capacity (reduced distance on test, shorter time and lower peak VO_2) than normal weight children.	
Kazuma et al. (2002) Examine relationship between HRV & age Case control	70 healthy (male only) 6-12yr Japanese **Weight** 12 obese, 53 normal, 5 thin (obese over 20%, normal 10-20%, thin under >10%).	LT ECG **Analysis** Holter FD (FF): LF, HF	**Reliability/validity** RR not equal so used cardiac curve using 3 % curve spline, instantaneous RR at 125ms & reconstructs each RR series of 512S. Hanning windowing function to measure spectral leakage **Inclusion/exclusion** If supreventricular premature contraction shorted than 80% of proceeding. No history of CV disease, hypertension, or other medical problems. **Other** PA not assessed or reported. HR values not reported.	**Statistics** One way ANOVA, Krustal Wallis Test **Weight & HRV** No difference in LF, HF (24hr, sleep or wake) between thin, normal & obese. LF:HF ratio no significant difference for 24hr, wake, sleep.	45%

Birch et al. (2012) To investigate the association between HRV and weight status in children. Case control	182 children 87males, 95 female 6-11yr **Group by weight** BMI (IOFF) Obese Normal weight	ST HRM (Sunnto) **Analysis** Kubios TD: RR interval, RMSSD, pNN50% FD (FF): LF, HF, LF:HF ratio	**Reliability/validity** NR **Inclusion/exclusion** NR **Other** Posture: supine Breathing not controlled Morning testing Temperature controlled PA not assessed or reported. RR interval values reported	**Statistics** Correlation between Pearson correlation t-test (HRV/ sex/weight) 2 by 2 ANCOVA (controlled for age) **Weight & HRV** TD: RMSSD, pNN50% significantly lower in overweight, obese children compared to normal weight (P<0.05). No difference in RR interval. FD: Overweight/obese significantly lower HF power compared to normal (P= 0.02). No difference in LF, HF:HF ratio (P>0.05) between groups, no gender differences were observed (P>0.05). *Correlation:* BMI significantly inversely related to RMSSD, pNN50% (P<0.01). No difference in frequency domain (LF and HF). *Data ANCOVA*: age significant as a covariate for RMSSD (P=0.014) RR interval (P=0.017) 1 year increase in age is associated with reduction of 9.4ms and increase 11.4ms for RMSSD and mean RR.	42%
Martini et al. (2001) To assess early signs of cardiac autonomic dysfunction (time & frequency domains) Case control	45 children 24 male, 21 female **Group by weight** Obese (<97$^{\%}$) using Rollan and Cachera (3yr pervious stable weight) 32 non diabetic obese (13.9 ± 1.7yr, 17 male, 15 female)	LT ECG **Analysis** Holter TD: SDNN,SDANN pNN50%, RMSSD FD (FF): LF, HF, (absolute & NU).	**Reliability/validity** Digital identification and labelling of QRS complex. **Inclusion/exclusion** Premature ventricular complexes & adjacent RR intervals, electrical noise were rejected by the software	**Statistics** Mann Whitney U test Spearman correlation **WEIGHT AND HRV** TD: RR interval, RMSSD & pNN50%, significant increase in non obese than obese (P<0.05). No difference in SDNN and SDANN. HR increased in obese (P=0.02).	36%

	13 matched healthy lean (12.9 ± 1.6yr, 7 male, 6 female)	LF: HF ratio	**Other** PA not assessed or reported. HR and RR interval values reported.	FD: LF (NU) was not significantly different between obese & non obese for day, night & 24hr. HF (NU) 24hr significant increase in non obese than obese (P=0.035) and increase at night in non-obese than obese (P=0.04). LF:HF ratio increase in obese than no obese (P=0.035) & night time (P=0.03) no difference for daytime.	
Riva et al. (2001) Case control	47 children **Group by weight** 23 non diabetic obese (13.9 ± 1.7yr) 14 sex matched lean (12.9 ± 1.6yr).	LT ECG **Analysis** Holter TD: mean NN, SDNN, SDANN, RMSSD, pNN50% FD (FF): LF, HF, (ms, NU), LF:HF ratio.	**Reliability/validity** NR **Inclusion/exclusion** NR **Other** PA not assessed or reported. HR values not reported**.**	**Statistics** t-test Mann Whitney U test Spearman rank **WEIGHT & HRV** TD: SDNN, SDANN, RMSSD, pNN50% was significantly higher in control than obese. FD: LF (NU) significantly higher 24hr & day in obese compared to control. No difference at night. HF (NU) no significant difference (24hr, day, night) between obese & control. LF:HF ratio significantly higher in obese for 24hr, day, night compared to control.	32%

BMI - body mass index, **CV** – cardiovascular, **ECG** – electrocardiogram, **FD** - frequency domain, **FF** - fast Fourier transform, **HF** - high frequency power, **HRM** - heart rate monitor, **HRV** - heart rate variability, **HR** - heart rate, hr – hour, **LF** - low frequency power, **LF:HF** - low frequency to high frequency ratio, **LT** - long term, **NDA** - normal daily activity, **NR** - not reported, **PSA** - power spectral density, **QIS** - quality index score, **S** – seconds, **TD** - time domain, **TP** - total power, **yr** - years.

Highlights

- We review the influence of childhood age and obesity on heart rate variability.
- During infancy parasympathetic activity increases relative to sympathetic activity.
- This trend continues throughout early-to-late childhood but at a reduced rate.
- Childhood obesity disrupts the normal maturation of cardiac autonomic control.
- Cardiac parasympathetic activity is decreased in obese children.